

16. (Previously Once Amended) The contrast agent of claim 1 wherein the physiologically acceptable gas is C_4F_8 .

18. (Previously Once Amended) The contrast agent of claim 1 wherein the physiologically acceptable gas is C_2F_6 .

19. (Previously Once Amended) The contrast agent of claim 1 wherein the physiologically acceptable gas is C_2ClF_5 .

23. (Previously Once Amended) The contrast agent of claim 1 wherein the physiologically acceptable gas is C_3F_8 .

27 (New) The contrast agent of claim 6, wherein the physiologically acceptable gas is selected from the group consisting of CF_4 , C_4F_8 , C_2F_6 , C_3F_8 and C_2ClF_5 .

REMARKS

The pending claims of the present application were substantially copied from the claims of U.S. Patent Nos. 5,573,751 ("751 patent") and 5,409,688 ("688 patent") as part of a request for interference with the '751 and '688 patents. Since the '751 and '688 claims were held allowable and the pending claims of the present application have an earlier effective filing date than any of the '751 and '688 patent claims, the pending claims here should be deemed allowable like the '751 and '688 patent claims and an interference should be declared therebetween.

Claims 1-7, 9, 14, 16, 18, 19, 23 and 27 are pending in this application.

Applicants thank the Examiner for the removal of the previous 35 U.S.C. §§ 112 and 102(b) rejections.

The Examiner stated that all of the pending claims have an effective priority date of the instant application. Office Action, pp. 2-3. Applicants respectfully traverse and submit that all

of the pending claims have an effective filing date of April 2, 1990, the filing date of EP 90810262.7.

Additionally, in the Office Action, the Examiner has rejected the pending claims 1-7, 9, 14, 16, 18, 19 and 23 under 35 U.S.C. §§ 102(e) and 103 as being anticipated and/or obvious in view of U.S. Patent No. 5,558,856 ("Klaveness"), U.S. Patent No. 5,776,429 ("Unger I"), U.S. Patent No. 5,585,112, ("Unger II"), U.S. Patent No. 5,558,094 ("Quay I") and U.S. Patent No. 5,393,524 ("Quay II"). The Examiner also rejected claims 1-7, 9, 14, 16, 18, 19 and 23 under 35 U.S.C. §§ 102(e) and 103 as being anticipated and/or obvious in view of U.S. Patent No. 5,716,597 ("Lohrmann"). Claims 1-7, 9, 14, 16, 18, 19 and 23 were also rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent No. 5,730,954 ("Albayrak") and U.S. Patent No. 5,593,687 ("Rossling I"). Applicants respectfully traverse.

Furthermore, the Examiner rejected claims 1-7, 9, 14, 16, 18, 19 and 23 under 35 U.S.C. § 103 as being unpatentable over U.S. Patent No. 5,501,863 ("Rössling II"); U.S. Patent No. 4,276,885 ("Tickner II"); U.S. Patent No. 4,265,251 ("Tickner I"); WO 90/12823 ("Illum"); U.S. Patent No. 5,730,954 ("Albayrak"); U.S. Patent No. 5,147,631 ("Glajch"); Swanson et al., "Enhancement Agents for Ultrasound Fundamentals," *Pharmaceuticals In Medical Imaging*, pp. 682-687 (1990) ("Swanson"); and U.S. Patent No. 4,466,442 ("Hillman") in view of Lincoff et al., "Intravitreal Longevity of Three Perfluorocarbon Gases," *Arch. Ophthalmology*, 98:1610-1611 (1980) ("Lincoff I"); Lincoff et al., "Invitreal Expansion of Perfluorocarbon Bubbles," *Arch. Ophthalmology*, 98:1646 (1980) ("Lincoff II"); Jacobs, "Intraocular Gas Measurement Using A-Scan Ultrasound," *Current Eye Research*, 5(8):575-578 (1986) ("Jacobs"); and "Freon' Fluorocarbons: Properties and Applications" in DuPont Technical Bulletin G-1 (E.I. duPont de

Nemours and Company, Wilmington, DE), pp. 1-10 (1987) ("DuPont"). Applicants respectfully traverse.

It is noted that thirteen references have been asserted as the basis of the Examiner's last obviousness rejection. As the courts have stated, the fact that it is necessary to cite such a large number of references is, in and of itself, indicative of non-obviousness. *Minneapolis-Honeywell Regulator Company v. Midwestern Instruments, Inc.*, 298 F.2d 36, 38, 131 USPQ 402, 403 (7th Cir. 1961; *The Ric-Wil Company v. E.B. Kaiser Company*, 179 F.2d 401, 404, 84 USPQ 121,124 (7th Cir. 1950); *Reynolds et al. v. Whiting Machine Works*, 167 F.2d 78, 83, 76 USPQ 551, 555 (4th Cir. 1948); and *Racal-Vadic, Inc. v. Universal Data Systems*, 1980 U.S. Dist. LEXIS 15864, *81, 207 USPQ 902, 927 (N.D. Ala. 1980). Indeed, the inference that can be taken from the large reference citation is that no one reference is on point and that the Applicants have clearly accomplished what the prior art has repeatedly failed to do. *Minneapolis-Honeywell Regulator Company v. Midwestern Instruments, Inc.*, 298 F.2d 36, 38, 131 USPQ 402, 403 (7th Cir. 1961).

I. Effective Priority Date

The Examiner stated that all of the claims have an effective priority date of March 5, 1999. Office Action, pp. 2-3. Applicants respectfully traverse. Applicants respectfully submit that all of the pending claims have an effective filing date of April 2, 1990, the filing date of EP 90810262.7. Specifically, the Applicants hereby address the Examiner's conclusion on the effective filing date of the following elements:

1. The inventive concept of using CF₄, C₄F₈, C₂F₆, C₂ClF₅, and C₃F₈ was first disclosed in EP 90810262.7 by the term "freon" (i.e., '262.7, p. 8). It is well known that CF₄, C₄F₈, C₂F₆, C₂ClF₅, and C₃F₈ are freons. See e.g., "'Freon' Fluorocarbons: Properties and Applications" in DuPont Technical Bulletin G-1 (E.I. duPont de Nemours and Company, Wilmington, DE), pp.1-10 (1987).

2. The inventive concept of using CF₄, C₄F₈, C₂F₆, C₂ClF₅, and C₃F₈ with a surfactant was first disclosed in EP 90810262.7 by the terms "freon" (i.e., '262.7, p. 8) and "surfactants" (i.e., '262.7, p. 5 "suspension being stabilized by the presence of the surfactants...", p. 8 "surfactants which are convenient in this invention...").

Thus, Applicants respectfully submit that the effective filing date of all of the pending claims in the instant application is April 2, 1990, the filing date of EP 90810262.7.

II. Schneider Claims 1-7, 9, 14, 16, 18, 19, and 23
Are Patentable Over Klaveness, Unger I, Unger II, Quay I and Quay II

The Examiner rejected claims 1-7, 9, 14, 16, 18, 19 and 23 under 35 U.S.C. §§ 102(e) and 103 as being anticipated by and obvious over Klaveness, Unger I, Unger II, Quay I and Quay

II. Applicants respectfully traverse.

A. Klaveness Is Not Prior Art
To Schneider Claims 1-7, 9, 14, 16, 18, 19, and 23

As explained above, each of the pending claims of the instant application has an effective priority date of April 2, 1990, the filing date of EP 90810262.7. Since Klaveness has a PCT publication date of July 22, 1993 and a 35 U.S.C. § 102(e) date of December 9, 1994, both of which are later than the effective filing date of the Applicants' claims, Klaveness is not prior art to the Applicants' claims. Thus, withdrawal of this rejection based on Klaveness is respectfully requested.

B. Unger I and Unger II Are
Not Prior Art To Schneider
Claims 1-7, 9, 14, 16, 18, 19, and 23

As stated above, each of the pending claims of the instant application has an effective priority date of April 2, 1990, the filing date of EP 90810262.7, which is prior to the earliest possible effective U.S. filing date of Unger I and Unger II. Applicants observe that both Unger I and Unger II mention some seven or more U.S. priority filing dates, most of which are

continuation-in-part applications which continue to add new matter to each previous priority application. Yet the Examiner does not specify which of these dates is being relied upon in the Office Action. Applicants have determined that the earliest possible effective filing date under 35 U.S.C. 102(e) is April 30, 1993 for Unger I and November 30, 1993 for Unger II, and wish the Examiner to confirm this determination. Thus, withdrawal of this rejection based on Unger I and Unger II is respectfully requested.

C. Quay I and Quay II Are Not
Prior Art To Schneider
Claims 1-7, 9, 14, 16, 18, 19, and 23

As already discussed above, each of the pending claims of the instant application has an effective priority date of April 2, 1990, the filing date of EP 90810262.7. Thus, Quay I and Quay II, which have an earliest possible effective U.S. filing date of September 17, 1991, is not prior art to the Applicants' claims. Thus, withdrawal of this rejection based on Quay I and Quay II is respectfully requested.

D. Schneider Claims 1-7, 9, 14, 16, 18, 19, and 23 are
Nonobvious And Patentable Over Klaveness,
Unger I, Unger II, Quay I And Quay II

The Examiner rejected Schneider claims 1-7, 9, 14, 16, 18, 19 and 23 over Klaveness, Unger I, Unger II, Quay I and Quay II under 35 U.S.C. § 103. However, as explained above, neither Klaveness, Unger I, Unger II, Quay I nor Quay II are prior art to the Schneider claims since Klaveness, Unger I, Unger II, Quay I and Quay II all have earliest possible effective filing dates later than the April 2, 1990 effective filing date of Schneider's claims. Thus, withdrawal of this rejection in view of Klaveness, Unger I, Unger II, Quay I and Quay II is respectfully requested.

III. Schneider Claims 1-7, 9, 14, 16, 18, 19, and 23
Are Patentable Over Lohrmann

The Examiner rejected claims 1-7, 9, 14, 16, 18, 19 and 23 under 35 U.S.C. §§ 102(e) and 103 as being anticipated by and obvious over Lohrmann. Applicants respectfully traverse.

As explained above, each of the pending claims of the instant application has an effective priority date of April 2, 1990, the filing date of EP 90810262.7. Since Lohrmann has an earliest possible effective filing date of June 4, 1993, which is later than the effective filing date of the Applicants' claims, Lohrmann is not prior art to the Applicants' claims. Thus, withdrawal of this rejection based on Lohrmann is respectfully requested.

IV. Schneider Claims 1-7, 9, 14, 16, 18, 19, and 23
Are Patentable Over Albayrak And Rossling I

The Examiner rejected claims 1-7, 9, 14, 16, 18, 19 and 23 under 35 U.S.C. § 103 as unpatentable over Albayrak and Rossling I. Applicants respectfully traverse.

As discussed above, each of the pending claims of the instant application has an effective priority date of April 2, 1990, the filing date of EP 90810262.7. Thus, Albayrak, which has an earliest possible effective U.S. filing date of February 25, 1991 and Rössling, which has an earliest possible effective U.S. filing date of December 31, 1991, are not prior art to the Applicants' claims. Thus, withdrawal of this rejection based on Albayrak and Rossling I is respectfully requested.

V. Schneider Claims 1-7, 9, 14, 16, 18, 19, and 23
Are Patentable Over Rossling II, Tickner I, Tickner II, Illum,
Albayrak, Glajch, Swanson, Hilmann In View Of
Lincoff I, Lincoff II, Gardner, Jacobs and Dupont

The Examiner rejected claims 1-7, 9, 14, 16, 18, 19 and 23 under 35 U.S.C. § 103 as being unpatentable over Rossling II, Tickner I, Tickner II, Illum, Albayrak, Glajch, Swanson,

Hilman in view of Lincoff I, Lincoff II, Gardner, Jacobs and Dupont. Applicants respectfully traverse.

At the outset, as discussed above, each of the pending claims of the instant application has an effective priority date of April 2, 1990, the filing date of EP 90810262.7. Thus, since Albayrak (February 25, 1991), Rössling II (February 11, 1991), Illum (September 5, 1991), and Glajch (April 30, 1991) all have earliest possible effective filing dates after April 2, 1990, they are not prior art to those Schneider claims which have an effective priority date of April 2, 1990.

Additionally, as discussed below, none of these references, alone or in combination with another, provide all of the elements of the Applicants' claims:

A. Rössling II (U.S. Patent No. 5,501,863)

Rössling II discloses rigid particulate microparticles formed from aldehydes which may be porous and are often crystalline. Rössling II also discloses the use of undenatured albumin as a coupling agent to attach to the surface of the aldehydes used to make the microparticles.

B. Tickner I (U.S. Patent No. 4,276,885)

Tickner I discloses free gas microbubbles dispersed in gelatin membranes, which are warmed and dissolved in order to release free gas microbubbles. The gelatin acts as a viscosity barrier to reduce coalescence of the free gas microbubbles.

C. Tickner II (U.S. Patent No. 4,265,251)

Tickner II discloses saccharide microparticle precursors which dissolve in the bloodstream to release free gas microbubbles. These saccharide microparticles are porous, crystalline, rigid, and preferably grinded.

D. Illum (WO 90/12923)

Illum discloses multi-chambered hollow microcapsules. These microcapsules are rigid, particulate structures which may be porous and preferably have multiple gas-filled chambers.

E. Albayrak (U.S. Patent No. 5,730,954)

Albayrak discloses crystalline cavitate or clathrate forming host/guest complexes which dissolve to release free gas microbubbles. Albayrak also discloses the use of undenatured albumin and phosphatidylcholine in the liquid vehicle as viscosity or thickening agents which do not form a microbubble stabilized in part by surfactant.

F. Glajch (U.S. Patent No. 5,147,631)

Glajch discloses microparticles made of inorganic material. These microparticles are porous and may be crystalline.

G. Swanson

Swanson only mentions the use of liquid fluorocarbon as an agent which reacts to form bubbles.

H. Hilmann (U.S. Patent No. 4,466,442)

Hilmann discloses a solution containing a selected amount of tenside, viscosity raising compound and gas.

I. Lincoff I, Lincoff II, Gardner, Jacobs (collectively, the Ocular Documents)

Each of these Ocular Documents are directed to the use of a single large fluorinated gas bubble as intraocular tamponades for the treatment of retinal tears or detachments in the eye. Specifically, these Ocular Documents discuss the desirability of free gas expansion within the eye - a property which teaches away from the use of fluorinated gas as ultrasound contrast agents since gas expansion in the bloodstream could lead to serious health effects (i.e., embolism) in the patient.

J. DuPont

While DuPont confirms that the term “freon” includes the gases of the Applicants’ claims, there is no teaching or suggestion in this bulletin that freon gases may be used in an ultrasound contrast agent.

H. Applicant’s Microbubbles

Rossling II, Tickner I, Tickner II, Illum, Albayrak, Glajch, Swanson, Hilmann, the Ocular Documents, and Dupont do not, individually or in combination, teach, suggest, or disclose the Applicants’ microbubbles comprising a freon or an organic compound containing one or more atoms and fluorine wherein the microbubbles are stabilized in part by a surfactant.

Furthermore, there is no teaching or suggestion of Applicants’ specific stabilized microbubbles of new claim 27 which are sufficiently stable and resistant to pressure changes that they survive in the bloodstream long enough that they may be peripherally intravenously injected, travel through the right heart, through the lungs, and into the left heart without substantially dissolving.

Thus, as there is no teaching anywhere in any of the above cited references of the elements of the Applicants’ claims, withdrawal of this rejection based on Rossling II, Tickner I, Tickner II, Illum, Albayrak, Glajch, Swanson, Hilmann in view of Lincoff I, Lincoff II, Gardner, Jacobs and Dupont is respectfully requested.

Therefore, as these pending claims 1-7, 9, 14, 16, 18, 19, 23 and 27 are fully supported in the specification and are fully patentable over any references cited, favorable action on these claims is requested. In view of the foregoing, Applicants respectfully request that the rejections of these claims be withdrawn and all pending claims allowed.

VI. Response To Obviousness-Type Double Patenting
And Provisional Obviousness-Type Rejections

Page 5 of the Office Action contains two rejections, the first alleging obviousness-type double patenting rejections over a listing of some 16 U.S. patents and the second alleging obviousness-type double patenting over a host of pending patent applications. No "conflicting claims" were specified so it is difficult if not impossible to determine which of the patents and patent applications are of concern. As agreed to by the Examiner, these issues will be held in abeyance until claims are indicated to be otherwise allowable in this application.

If there are any further points requiring attention prior to allowance, the Examiner is asked to contact Applicant's counsel.

No fee is required. If there are additional fees, please charge them to our firm Deposit Account No. 14-1140.

Respectfully submitted,



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